(19)

THE PATENT OFFICE

2nd M. S. O. BUILDING
234/4, ACHARYA JAGADISH CHANDRA BOSE ROAD
CALCUTTA—700 020.

179788

INDIAN PATENT SPECIFICATION

(51) Int. Cl[1] : C 07 D 47/04
A 61 K 31/44

(52) Ind. Cl. : 32 F-1
55 E-4

A

(11) Document No. 179788 IN

Date of Document : 10.02.92

(42) Date of Publication : 06-12-97

(21) Application No. : 102 DEL 92

(22) Date of filing: 10.02.92

(71) Applicant : COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, Rafi Marg, New Delhi-110001, India, an Indian registered body incorporated under the Registration of Societies Act (Act XXI of 1860).

(72) Inventor : KANWAL RAJ, INDIAN
SURENDRA PAL VISHNOI, INDIA
ABOO SHOEB, INDIA
DEOKI NANDAN GUPTA, INDIA
GOVIND KESHRI, INDIA
VED PRAKASH KAMBOJ, INDIA

(74) Agent :

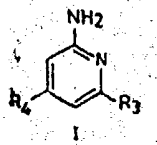
Claims : 3

Text : Pages ; Drgs. Sheets.
8 1

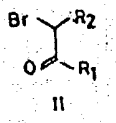
Examiner : HARDEV KARAR

(54) Title : A PROCESS FOR THE PREPARATION OF NOVEL 2-SUBSTITUTED AND 2,5,7-TRI-SUBSTITUTED IMIDAZO-(1,2-a)PYRIDINES SHOWING ANTIFERTILITY ACTIVITY.

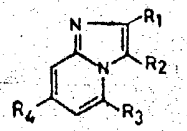
(57) Abstract : A process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines of the formula III, where R_1 represents substituted phenol such as halophenyl preferably chloro or bromo phenyl, methyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl; R_2=H; R_3=R_4=H or CH_3, which comprises refluxing correspondingly substituted 2-aminopyridines of formula I where R_3 & R_4 represent hydrogen or methyl groups with correspondingly



I



II



III

EX 104

PRICE : THIRTY RUPEES

1-5

substituted - bromoketone of the formula II where R_1 represents substituted phenol such as halophenyl preferably chloro or bromophenyl, alkyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl ; R_2=H; in the presence of an appotic solvent for a period ranging from 2-24 hrs. at a temperature in the range 36^0-90^0C and recovering the 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines, of formula III by conventional methods.

This invention relates to a process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo-(1,2-a) pyridines.

The novel 2-substituted and 2,5,7 trisubstituted imidazo-(1,2-a) pyridines prepared by the process of present invention have the formula III shown in the drawing accompanying this specification where R_1 represents substituted phenyl such as halophenyl, preferably chloro or bromo phenyl, methyl phenyl, nitro phenyl hydroxy phenyl, methoxy phenyl, ethoxyphenyl , carboxymethyl & carbethoxymethyl; R_2 = H ; R_3 = R_4 = H or CH_3

The compounds of the formula III prepared by the process of the present invention found to be useful as antiimplantation abortifacient agents. These compounds when tested in hamster for antifertility activity showed 30-100% protection against pregnancy at 2.5 - 20 mg / kg by oral and subcutaneous routes.

Accordingly, the present invention provides a process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines of the formula III shown in the drawing accompanying this specification, where R_1 represents substituted phenol such such as halophenyl preferably chloro or

bromo phenyl, methyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl; R_2 = H; R_3 = R_4 = H or CH_3, which comprises refluxing correspondingly substituted 2-aminopyridines of formula I where R_3 & R_4 represent hydrogen or methyl groups with correspondingly substituted - bromoketone of the formula II where R_1 represents substituted phenol such as halophenyl preferably chloro or bromophenyl, alkyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl ; R_2 =H; in the presence of an aprotic solvent for a period ranging from 2-24 hrs. at a temperature in the range 36 -90 °C and recovering the 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines, of formula III by conventional methods.

In a preferred embodiment of the invention the solvent used may be selected from chloroform dichloromethane, benzene THF and the like.

The compounds of the formula III prepared by the process of the invention, where R_1 represents 2 / 3 / 4 - OHC_6H_4 and R_2, R_3 & R_4 represent hydrogen are also

useful for the preparation of compounds of the formula IV i.e. the corresponding ethers of the formula III by treating with appropriate halides.

This process has been made subject matter of the copending application No.104/DEL/92

In yet another pending co-application No.103/DEL/92 we have described a process for the preparation of compounds of the formula V where R_1 represents bromophenyl (4-Br-C_6H_4), R_2 represents diethylaminomethyl, cyclic amino methyl; R_3 & R_4 represents hydrogen, starting from the compounds of the formula III, prepared by the process of the present invention. Compounds of the formula IV & V possess antifertility activity.

The invention is further illustrated by the examples given below which should not, however, be construed to limit the scope of the present invention.

EXAMPLE 1

2-(4-Hydroxyphenyl)imidazo[1,2-a]pyridine hydrobromide of formula III where R_1 represents 4-hydroxyphenyl, R_2,R_3 and R_4 represent Hydrogen

A solution of 4-hydroxyphenacyl bromide (215 mg, 1 mmol) and 2-aminopyridine (94 mg, 1 mmol) in chloroform (10 ml) was refluxed at 95° for 10 hr. On removal

of the solvent, the residue was heated at the same temperature for 0.5 hr. and crystallised from a mixture of $CH_3OH/CHCl_3$. The title compound, 210 mg, m.p. 231-32°C was obtained in 72% yield.

EXAMPLE 2

2-(4-Bromophenyl)-5,7-dimethylimidazo-[1,2-a]pyridine hydrobromide of formula III where R_1 represents 4-Bromophenyl, R_2, Hydrogen, R_3 & R_4 methyl

A solution of 4-bromophenacyl bromide (278 mg, 1 mmol) and 2-amino-4,6-dimethyl pyridine (122 mg, 1 mmol) was refluxed in chloroform (20 ml) at 80°C for 20 hr. On removal of the solvent, the residue was heated at the same temperature under vacuo for 1/2 hr. and crystallised from MeOH/ether. The title compound, m.p. 168-69°, was isolated in 50% yield.

EXAMPLE-3

2-(2-Hydroxyphenyl)imidazo[1,2-a]pyridine hydrobromide of formula III where R_1 represents 2-hydroxyphenyl, R_2,R_3,R_4 represent hydrogen

A solution of 2-hydroxyphenacyl bromoide (215 mg 1 mmol), 2-aminopyridine (94 mg, 1 mmol) was refluxed in chloroform for 24 hr. The residue obtained after removal

of solvent was crystallised from ethanol, m.p. 241-43°. The title compound was obtained in 50% yield.

EXAMPLE-4

2-(2-Hydroxyphenyl)-imidazo[1,2-a]pyridine hydrobromide of formula III where R_1 represents 2-hydroxyphenyl; R_2,R_3,R_4 represent hydrogen

A solution of 2-hydroxyphenacyl bromide (215 mg, 1mmol), 2-aminopyridine (94 mg, 1 mmol) was refluxed in methylene chloride (30 ml) at 50° for 10 hr. After removal of the solvent, the residue was crystallised from ethanol/ether, m.p. 241-43°. The title compound was obtained in 40% yield.

EXAMPLE-5

2-Carbethoxymethyl-imidazo[1,2-a]pyridine of formu' III, where R_1 represents carbethoxymethyl-; R_2,R_3, R_4 represent hydrogen

A mixture of 2-aminopyridine (2.82 g; 0.03 mol) and 4-bromo-3-oxo-butanoic acid ethyl ester (6.27 g; 0.03 mol) was refluxed in $CHCl_3$ (50 ml) for 3 hr. On removal of the solvent, the residue was heated at 100°C for 1 hr, neatralized with NH_4OH, extracted with $CHCl_3$ and dried (Na_2So_4). The solvent removed and the residue purified on Si-gel column using 2% methanol in $CHCl_3$ (V/V). The title compound (2.4 g) was obtained as a semi-solid mass in 40% yield.

WE CLAIM:-

1. A process for the preparation of novel 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines of the formula III shown in the drawing accompanying this specification, where R_1 represents substituted phenol such such as halophenyl preferably chloro or bromo phenyl, methyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl; R_2 = H; R_3 = R_4 = H or CH_3, which comprises refluxing correspondingly substituted 2-aminopyridines of formula I where R_3 & R_4 represent hydrogen or methyl groups with correspondingly substituted - bromoketone of the formula II where R_1 represents substituted phenol such as halophenyl preferably chloro or bromophenyl, alkyl phenyl, nitro phenyl, hydroxy phenyl, methoxy phenyl, ethoxy phenyl or carboxymethyl & carbethoxymethyl ; R_2 =H; in the presence of an aprotic solvent for a period ranging from 2-24 hrs. at a temperature in the range 36 -90 ^{0}C and recovering the 2-substituted and 2,5,7 trisubstituted imidazo (1,2-a) pyridines, of formula III by conventional methods.

2. A process as claimed in claim 1 wherein solvent used is selected from chloroform, dichloromethane, benzene, THF.

3. A process for the preparation of novel 2-substituted and 2,5,7 tri substituted imidazo (1,2-a) pyridines of the formula III as defined in the claim 1 substantially as herein described with reference to the examples.

Dated this 10th day of Feb.,1992

Balashmi

(Mrs. L.Balasubrahmanyam)

Scientist (Patents)

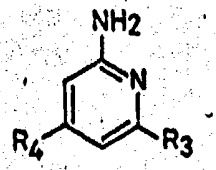
Council of Scientific & Industrial Research

179788

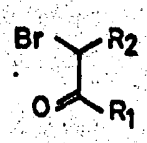
Council of Scientific and Industrial Research

APPL NO. 102/DEL/92

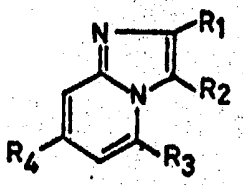
No. of Sheets: 1
Sheet No 1



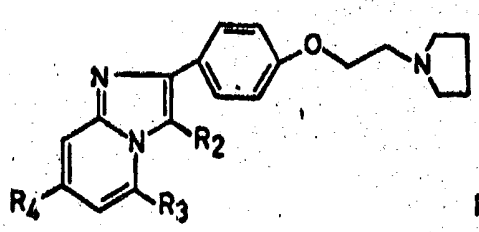
I



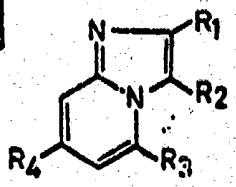
II



III



IV



V

N. R. Srinivasan

(APPLICANTS)